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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/635,196	08/06/2003	David Warburton	9022-21CT	8327

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MYERS BIGEL SIBLEY & SAJOVEC
PO BOX 37428
RALEIGH, NC 27627

EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 11/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/635,196	WARBURTON ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 3-5, 7, 9, 10, 13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,7,9,10,13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *8/6/03* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/19/05,8/6/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Non-Final Rejection

Claims 1, 3-5, 7, 9, 10 and 13 are pending.

The amendment to claims 1, 3, 4, 5, 7, 9, and 10, the addition of claim 13, and the cancellation of claims 2, 6, 8, and 11-12 in paper filed on 8/6/03 is acknowledged and considered by the examiner.

The examiner is considering the supplemental European search report but will not initial it on the PTO-1449 because it is not considered a published document.

Priority

The status of the parent application is missing on the first of the instant specification.

In addition, the provisional application listed in the specification does not have the same number as the provisional application listed on the bib sheet and oath.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 4, 5, 7, 9, 10, and 13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled

in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

New Matter rejection:

Amended claim 1 (and claims dependent therefrom) filed on 8/6/03 introduces new subject matter into the application.

With respect to the limitation 'alveolar epithelial progenitor cells' in amended claim 1 and claims dependent therefrom, the original specification did not disclose the limitation. With respect to the limitation 'alveolar epithelial progenitor cells are lungs cells' in amended claim 9, the original specification did not disclose the limitation. With respect to the limitation 'alveolar epithelial progenitor cells are bone marrow cells' in amended claim 10, the original specification did not disclose the limitation. Applicant has not pointed out where the amended claims are supported, nor does there appear to be a written description of the claim limitations in the application as filed. See MPEP § 2163.06.

It is apparent that the applicants at the time the invention was made did not intend or contemplate making and/or using alveolar epithelial progenitor cells recited in amended claims and claims dependent therefrom as part of the disclosure of their invention. There is no evidence in the specification that the applicants were possession of the alveolar epithelial progenitor cells as set forth in the amended claims and claims dependent thereof, as it is now claimed, at the time the application was filed.

"It is not sufficient for purposes of the written description requirement of Section 112 that the disclosure, when combined with the knowledge in the art, would lead one to speculate as to

modifications that the inventor might have envisioned, but failed to disclose." *Lockwood v. American Airlines Inc.*, 41 USPQ2d 1961, 1966 (CAFC 1997).

Claims 1, 3-5, 7, 9, 10, and 13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 3-5, 7, 9, 10, and 13, as best understood, are readable on a genus of alveolar epithelial progenitor cells capable of regenerating lung alveolar surface, wherein the genus of progenitor cells are not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification contemplates using a genus of progenitor or stem cells capable of regenerating lung alveolar surface. Furthermore, the specification contemplates that a species of stem/progenitor cells exist in the distal lung and can regenerate both alveolar epithelium and capillaries. The invention contemplates exploiting the properties of the stem cells by stimulating them to divide and differentiate using soluble growth factors and other suitable growth factors (see page 9 of the specification). However, the specification only discloses *in vitro* embryonic day 12 (E12) lung cells cultured with FGF-10 and lung sections from embryonic and neonatal

mice and hyperoxia treated adult rats express telomerase that plays a role in directional outgrowth and possibly induction of epithelial buds and AEC2 cells have been designated the primary progenitor cell of the alveolar epithelium. The limitation in instant claims 9 and 10 indicate that the genus is broader than progenitor cells from lung cells (e.g., AEC2) or bone marrow cells. The art of record displays a table of stem cells and the type of cell types developed and none of the stem cells developed into lung cells (NIH: News: Stem Cells; Stem Cells; Scientific Progress and Future Research Directions [online], June 2001, Appendix D, http://www.nih.gov/news/stemcell/scireport.htm, retrieved on 5/15/02). The specification does not disclose how to obtain or make a representative number of progenitor cells that can regenerate lung alveolar surface. It is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or cells that are essential for the genus of progenitor cells as claimed; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of progenitor cells that must exhibit the disclosed biological functions as contemplated by the claims.

It is not sufficient to contemplate a genus of alveolar epithelial progenitor cells to support the present claimed invention directed to a genus of progenitor cells capable of regenerating lung alveolar surface. The claimed invention as a whole is not adequately described if the claims require essential or critical elements, which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Claiming a genus of progenitor cells that must possess the biological properties as contemplated by applicant's

disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of progenitor cells that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Claims 1, 3-5, 7, 9, 10, and 13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The field of the invention embraces a method of stimulating the growth of lung alveolar surface in a lung of a mammal comprising: providing progenitor cells capable of regenerating lung alveolar surface; and administering said cells to said lung (complete or a fraction of a lung) in an amount sufficient to stimulate the growth of the lung alveolar surface.

The state of the art for tissue restoration displays that cell transplants have been used in several areas, (Stocum et al., Wound Rep Reg, Vol. 6, pp. 276-290, 1998). Stocum teaches that over the past 50 years, we have made progress in our ability to replace body parts with devices, solid organs, and tissue transplants, or both (page 277). Such replacement parts, however, still pose significant biological problems, and they are not useful for all situations (page 277). Furthermore, Stocum teaches that providing reliable sources of cells for cell transplant is crucial issue that requires establishing culture banks or proliferating stem, progenitor, or differentiated cells that can be drawn on as required, as well as cell culture media that support the proliferation and differentiation of these cells (page 284).

Furthermore with respect to lung transplantation, the state of the art for lung transplantation has gained widespread acceptance as a therapeutic option for a diverse array of lung diseases as taught by Arcasov et al. (Medical Progress, Vol. 340, pages 1081-1091. Nonetheless, complications are frequent and result constraints on long-term preservation of graft function and patient survival (page 1081). The common complications are primary graft failure, airway complications, infection, acute rejection, and chronic rejection (pages 1087-1088). Lung transplantation that reaches its current clinical plateau largely through refinements in the selection of patients, operative techniques, and postoperative care (page 1088). Two major hurdles must be overcome to increase the applicability of lung transplantation and improve long-

term results: the supply of donor organs must be increased to meet the demand, and chronic rejection must be more effectively prevented (page 1088).

In addition, with respect to lung stem cells, the state of the art as exemplified by Magdaleno et al., (Adv Pediatr, Vol. 45, pp. 363-96, 1998), Magdaleno teaches that before stem cells can used for therapeutic purposes understanding tissue genetics and immunology is essential (pages 363-364). Animal models or repair provide some clues about which cells are the stem cells in the lung (page 373). However, this approach is complex and oftentimes it is difficult to identify the specific molecular events that govern lung cell gene expression (page 373). In the course of studying the evidence for specific stem cells in the lung, one consensus perpetually emerges: the processes of lung development, gene regulation, and injury repair are multi-step processes involving a concerted effort between extracellular and intracellular input to elicit proliferation and/or differentiation of specific epithelial cell types of the airways (page 388). Wu further supports the unpredictability of lung stem cells and progenitor cells (Stem Cells and Development 13:607-613, 2004).

The disclosure provides working examples: Example 1 (pages 10-16) displays that exogenous fibroblast growth factor 10 (fgf10) can stimulate wild type lung morphogenesis and rescues cells that were exposed to nitrogen in an *in vitro* cultures of murine lung cells. Example 2 (pages 16-22) encompasses hyperoxia treatment of adult rat and fetal rat alveolar epithelial type 2 cells (AEC2) isolated in cell cultures. The results from example 2 show that telomerase activity is observed in rat fetal AEC2 and can be re-induced in adult AEC 2 following hyperoxic injury. Furthermore, the disclosure contemplates a method of inducing lung regeneration by autologous stem cell replacement, wherein the stem cells are genetically modified (pages 9-10).

The specification states that AEC2 cells AEC2 cells have been designated the primary progenitor cell of the alveolar epithelium (page 3). The specification provides sufficient guidance for one skilled in the art to use exogenous fgf10 to stimulate growth in an *in vitro* culture of murine lungs cells. However, this does not reasonably extrapolate to the claimed invention because the specification fails to provide sufficient guidance in several critical areas which encompass: 1) how to make and/or use a genus of progenitor cells in the method of the claimed invention, 2) how to determine what progenitor cells are capable of regenerating lung alveolar surface, 3) how to remove a lung or portion thereof, 4) how to administer said cells to said lung or portion thereof, 5) what amount is sufficient to stimulate the growth of lung alveolar surface, 6) how to avoid a graft vs. host response in a mammal undergoing a lung transplant, and 7) how to transplant a lung into a mammal. The specification fails to provide sufficient guidance for how stimulating murine lung cells *in vitro* can reasonably correlate to any method for treating a mammal that needs growth of the lung alveolar surface using progenitor cells in a method of cell therapy. In view of the art of record, which teaches, "drawing analogies from the studies performed in rodents to human lung development raises certain caveats, however, because lung development in humans differs from that observed in rodents, See pages L1197-L1198 (Driscoll et al., Am J Physiol Lung Cell Mol Physiol, Vol. 279, pp. 1191-98, 2000)." Furthermore, Driscoll teaches that, "the data presented in the disclosure raises question to whether telomerase expression in the repairing lung is simply a marker for proliferation and whether it is expressed more ubiquitously than would be expected for a stem cell population (page L1196)." In addition, Driscoll teaches that, "because no method exist at the time the application was filed and currently for following the fate of individual cells in the lung, it is impossible to determine when and how

telomerase expression is induced an how long it persists in each individual cell (page L1197)." In view of In Re Wands Factors, it would take one skilled in the art an undue amount of experimentation to reasonably correlate from the disclosure to any progenitor cell therapy method for stimulating the growth of the lung alveolar surface in a mammalian lung for a therapeutic result. In view of the concerns stated by the art of record, the specification does not provide sufficient guidance for one skilled in the art to make and/or use a genus of progenitor cells in any method of stimulating the growth of lung alveolar surface in any mammal's lung. Thus, in view of the In re Wands Factors, the disclosure is not enabled for the claimed invention.

In addition, with respect to claims 1, 3-5, 7, 9, 10, 13, the specification fails to provide what progenitor cells are capable of regenerating lung alveolar surface in any mammal. The specification states that, "there are stem cells in the distal portion of the lung that can regenerate alveolar epithelium," however, the disclosure fails to provide sufficient guidance for what cells are capable of regenerating alveolar epithelium. The specification contemplates that any growth factor may be used to carry out the claimed invention and cites art of record (page 9), which list several growth factors. However, the specification and the art of record do not list what growth factors are required to make the progenitor cells into cells that can be used in any method to stimulate the growth of lung alveolar surface. In view of the art of record (Stocum, pages 284-285), one skilled in the art understands that culturing stem cells into specialized cells (e.g. lung alveolar surface cells) would require an undue amount of experimentation in view of the art of record and the disclosure, since neither provides sufficient guidance for what growth factors and culture media is required to culture and support the proliferation and differentiation of any cells into cells that could be used in a method of stimulating the growth of lung alveolar surface.

Furthermore, with respect to using a genus of progenitor cells in any ex vivo method of cell therapy for stimulating the growth of lung alveolar surface, the specification fails to provide sufficient guidance for what type of progenitor cells are capable of regenerating lung surface and how to circumvent the problem with the mammal's immune system when the mammal is exposed to allogenic, xenogenic, or a genetically modified lung or portion thereof. See Stocum page 285, **Evasion of the immune system** and Arcaso, page 1086-1088, **common complications**.

In conclusion, the specification and claims coupled with the state of the art at the time the invention was made do not provide reasonable enablement for the claimed invention. In view of the state of the art for lung transplantation, stem cell therapy, wherein the stem cells are used in a cell therapy method, wherein the method is employed to correct a genetic disorder in any mammal was unpredictable at the time the invention was made, the lack of sufficient guidance to any therapeutic method of stem cell therapy, the breadth of the claims, one skilled in the art could not make and/or use the invention without undue experimentation.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, acting SPE – Art Unit 1635, can be reached at (571) 272-0811.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal

Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Brian Whiteman
Patent Examiner, Group 1635